Spontaneous action potential initiation by fast and slow stochastic ion channels

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Abstract

A stochastic version of the Morris–Lecar model is formulated, where the noise originates from stochastic ion channels. Instead of using a Langevin approximation, each population of ion channels [Sodium (Na^+) and Potassium (K^+)] is modeled as a discrete birth-death process. The birth rate is voltage dependent, and the voltage changes deterministically between jumps in the number of open ion channels, making the hybrid stochastic process nonlinear. The classic Morris–Lecar model, recovered in the deterministic limit, is an excitable system, and transient spikes in voltage are called action potentials. Ion channel noise can initiate spontaneous action potentials. In the deterministic setting, K^+ channel dynamics are slow and the fraction of open K^+ channels is assumed to be fixed on the time scale of action potential initiation. The validity of this assumption in the stochastic setting is examined using a systematic perturbation analysis. We find that in most physically relevant cases, this assumption breaks down.

1 Introduction

Any understanding of brain function must include the role of noise. Neural networks possess the ability to perform complex computations—taking advantage of noise when possible, while still performing reliably. To correctly characterize the structure and properties of noise in a network, we must first understand its source.

Broadly speaking, a given neuron within a network receives input from two main sources of noise. The first is background synaptic activity, such as experienced when trying to have a conversation in a crowded restaurant, and this noise is a network level phenomenon. The second is spontaneous activity due to thermal fluctuations affecting cellular physiology, and this noise is intrinsic to each neuron.

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One source of intrinsic noise is ion channel fluctuations [16]. Sodium (Na^+) and Potassium (K^+) ion channels randomly shift between open and closed conformations due to the effects of thermal fluctuations, and the rate at which channels switch state depends on the membrane voltage. The voltage dependent activity of ion channels gives rise to membrane excitability. Excitable systems are widely studied in neuroscience, chemical reactions, lasers, and climate dynamics [9].

Once the voltage crosses a certain threshold, a transient spike in voltage is initiated, called an action potential. Ion channel noise can lead to spontaneous action potentials (SAPs), which can have a large effect on network function. If SAPs are too frequent, a neuron cannot reliably perform its computational role. Hence, ion channel noise imposes a fundamental limit on the density of neural tissue. Smaller neurons must function with fewer ion channels, making ion channel fluctuations more significant and more likely to cause a SAP. The effect of spontaneous activity on the reliability of a neuron can be quantified using information theory [14], but the relationship between ion channel noise and spontaneous activity remains unresolved.

In the Morris–Lecar (ML) model of a neuron [10], there is no well-defined voltage threshold for initiation of an action potential, but an effective threshold can be derived using a fast/slow analysis. In most cases, K^+ channels open and close slowly compared to Na^+ channels (Ca^{2+} channels in the original model), and the voltage response to changes in the fraction of open Na^+ channels is so fast that the fraction of open K^+ channels remains relatively constant. However, it is not clear if the fast/slow analysis is valid in a stochastic setting. In this letter, we show using a systematic perturbation analysis that the fast/slow analysis is not generally valid for initiation of a SAP. Furthermore, our analysis of the stochastic system leads to a well defined threshold for action potential initiation, allowing for the formulation of an exit time problem in an excitable system.

Deterministic single neuron models, such as the Hodgkin-Huxley model, are useful tools for understanding the mechanism of membrane excitability [7]. These models assume a large population of ion channels so that their effect on membrane conductance can be averaged. As a result, the average fraction of open ion channels modulates the effective ion conductance, which in turn depends on voltage. The ML model can be understood as a simplified version of the Hodgkin-Huxley model and provides a mechanism for the action potential. The deterministic ML equation is

$$\begin{aligned} C_{\mathrm{m}}\dot{v} &= x_\infty(v) f_{\mathrm{Na}}(v) + w f_{\mathrm{K}}(v) + f_{\mathrm{leak}}(v) + I_{\mathrm{app}} \\ \dot{w} &= \frac{w_\infty(v) - w}{\tau_w(v)}, \end{aligned} \tag{1}$$

where v is the membrane voltage, $f_i(v) = g_i(v_i - v)$ determine the ionic currents, w is the fraction of open K^+ channels, and $x_\infty(v) = (1 + \tanh(2(\gamma_{\mathrm{Na}} v + \kappa_{\mathrm{Na}})))/2$ is the fraction of open Na^+ channels, assumed to be at quasi-steady state. The steady state for w is

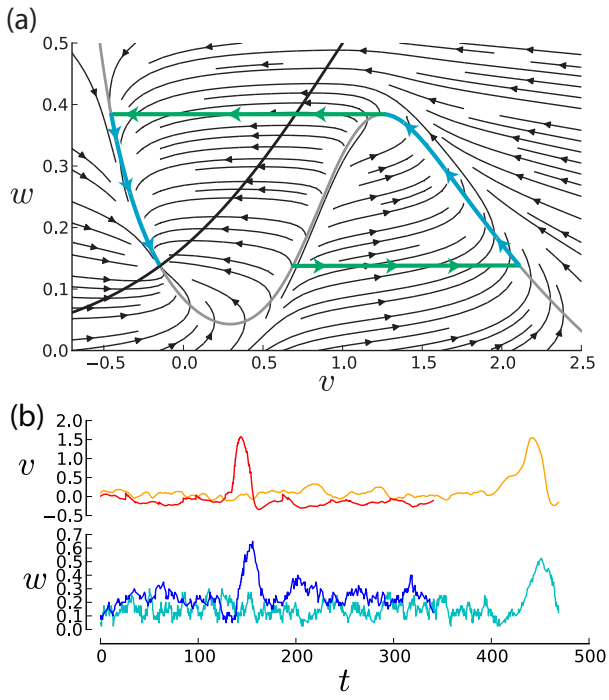

Figure 1: (a) Deterministic phase plane dynamics. Thick curves show the nullclines: $\dot{v} = 0$ as grey and $\dot{w} = 0$ as black. Black streamlines represent deterministic trajectories. Green/blue curves represent an action potential trajectory in the limit of slow w. (b) Representative stochastic trajectories showing spontaneous action potentials. Stochastic K^+ and Na^+ channels: red for voltage $v(t)$ and blue for the faction of open K^+ channels, $w(t)$. Stochastic K^+ and deterministic Na^+: orange for voltage $v(t)$ and light blue for $w(t)$.

$w_\infty(v) = (1 + \tanh(2(\gamma_K v + \kappa_K)))/2$, and the time constant $\tau_w(v) = 2\beta_K \cosh(\gamma_K v + \kappa_K)$ is generally assumed to be large so that the w dynamics are slow compared to v. We nondimensionalize voltage so that $v \to (v + v_{\text{eff}})/v_{\text{eff}}$, where $v_{\text{eff}} = \frac{|g_K \varphi v_K + g_l v_l|}{|g_K \varphi + g_l|}$. Parameter values are listed in Appendix A.

The standard deterministic analysis of an action potential using the ML model exploits the separation of time scales. Assume that $\dot{w}$ is small, and fix $w = w_0$ constant. The resulting voltage equation is bistable, with a stable steady state representing the resting potential, an unstable steady state representing the voltage threshold, and a stable steady state representing the excited state. In Fig. 1a, the phase plane dynamics of the system is shown. The colored curves that alternate green and blue show the action potential trajectory in the limit of slow w. The thick green line at $w = w_0 \approx 0.13$ shows the initiation phase of the action potential trajectory. Once the excited state is

reached at the $\dot{v}$ nullcline (grey curve), the slow w dynamics (blue curve) take over. This process continues until the trajectory eventually ends at the fixed point. To initiate a SAP, noise must perturb the voltage from the fixed point to the starting point of the action potential trajectory.

Past efforts to understand the relationship between SAP and ion channel noise focus on a Langevin (or diffusion) approximation. As a first approximation, one can add white noise to a given deterministic equation, such as the ML model (1). A more accurate method is to systematically derive a Langevin approximation from a more detailed model of ion channel fluctuations [3]. However, as recently shown in Ref. [6], Langevin approximations break down when considering metastable dynamics such as initiation of a SAP. Moreover, both studies make the same fast/slow approximation used to study action potential initiation in the deterministic model.

To consider SAP initiation, one might first add Na^+ channel noise, but keep the slow K^+ channels fixed as in the deterministic analysis. Voltage fluctuations caused by stochastic Na^+ can cause a metastable transition from the resting potential over the unstable voltage threshold, initiating a SAP. The stochastic initiation of a SAP then reduces to a familiar problem: exit from a potential well [6]. Fixing w constant is valid for the deterministic analysis, but even if average K^+ channel activity is slow, how do K^+ channel fluctuations affect SAP initiation? Monte-Carlo simulations of the ML neuron with stochastic K^+ channels (see Fig. 1b) show that SAP can be generated by K^+ channel noise alone, without Na^+ channel noise. If w is not held constant, the deterministic system has only one fixed point (at the resting voltage) and no longer has a well defined voltage threshold (see Fig. 1a). Therefore, we are immediately faced with a dilemma if we hope to reduce the problem to an exit from a potential well. How does one formulate an exit time problem in an excitable system with no clearly-defined threshold? If the system is close to a saddle-node bifurcation or if w is very slow, one can extrapolate a threshold called a ghost separatrix [8]; however, this definition does not hold in general and is not an intrinsic property of the excitable stochastic system.

To answer these questions, we apply recently developed perturbation techniques [1, 6, 11–13] to the full, discrete stochastic ML model. We find that through a stochastic analysis of the ML model, there is a well defined threshold for SAP, which does not exist in the deterministic model. Furthermore, we find that, in general, w is most likely not constant during initiation of a SAP.

2 Stochastic Model

A stochastic version of the ML model is formulated as follows. The voltage equation with $n = 0, 1, \cdots, N$ open Na^+ channels and $m = 0, 1, \cdots, M$ open K^+ channels is

$$\dot{V} = I(v, m, n) \equiv \frac{n}{N} f_{\text{Na}}(v) + \frac{m}{M} f_{\text{K}}(v) + f_{\text{leak}}(v) + I_{\text{app}}. \tag{2}$$

We assume that each channel is either open or closed and switches between each state according to

$$O \underset{\beta_i b_i(v)}{\overset{\beta_i a_i(v)}{\rightleftarrows}} C, \quad i = \mathrm{Na},\ \mathrm{K}, \tag{3}$$

where the transition rates are $a_{\mathrm{Na}}(v) = e^{4(\gamma_{\mathrm{Na}} v + \kappa_{\mathrm{Na}})}$, $b_{\mathrm{Na}} = 1$, $a_{\mathrm{K}}(v) = e^{\gamma_{\mathrm{K}} v + \kappa_{\mathrm{K}}}$, and $b_{\mathrm{K}}(v) = e^{-\gamma_{\mathrm{K}} v - \kappa_{\mathrm{K}}}$. We assume that the Na^+ channels open and close rapidly, so that $1/\beta_{\mathrm{Na}} \ll \tau_m$, where $\tau_m = C_{\mathrm{m}}/g_{\mathrm{L}}$ is the membrane time constant. Taking m and n in (2) to be stochastic birth/death processes, we obtain a stochastic hybrid process, which we formulate in terms of the probability density function, $p(v, m, n, t)$; it satisfies the differential Chapman–Kolmogorov (CK) [5] equation,

$$\frac{\partial}{\partial t}\rho(v, m, n, t) = -\frac{\partial}{\partial v}(I(v, m, n)\rho) + \beta_{\mathrm{K}}\mathbb{L}_{\mathrm{K}}\rho + \beta_{\mathrm{Na}}\mathbb{L}_{\mathrm{Na}}\rho, \tag{4}$$

The jump operators,

$$\mathbb{L}_{\mathrm{Na}} = (\mathbb{E}_n^+ - 1)\Omega_{\mathrm{Na}}^+(n|v) + (\mathbb{E}_n^- - 1)\Omega_{\mathrm{Na}}^-(n|v), \tag{5}$$

and

$$\mathbb{L}_{\mathrm{K}} = (\mathbb{E}_m^+ - 1)\Omega_{\mathrm{K}}^+(m|v) + (\mathbb{E}_m^- - 1)\Omega_{\mathrm{K}}^-(m|v), \tag{6}$$

govern opening/closing of Na^+ and K^+ channels, respectively, with $\mathbb{E}_a^{\pm} f(a) = f(a \pm 1)$, $\Omega_{\mathrm{Na}}^+(n|v) = n$, $\Omega_{\mathrm{Na}}^-(n|v) = (N - n)a_{\mathrm{Na}}(v)$, $\Omega_{\mathrm{K}}^+(m|v) = m a_{\mathrm{K}}(v)$, and $\Omega_{\mathrm{K}}^-(m|v) = (M - m)b_{\mathrm{K}}(v)$.

The deterministic system (1) is recovered in the limit $\beta_{\mathrm{Na}} \to \infty$, $M \to \infty$, and we assume that the limit is taken with $\lambda_M = \beta_{\mathrm{Na}}/M$ fixed. After setting $w = m/M$, the limit yields $x_\infty(v) = a_{\mathrm{Na}}(v)/(1 + a_{\mathrm{Na}}(v))$ and $w_\infty(v) = a_{\mathrm{K}}(v)/(b_{\mathrm{K}}(v) + a_{\mathrm{K}}(v))$, which is consistent with the deterministic definition.

The parameter β_{K} determines how rapidly the K^+ channels fluctuate. Previously, the authors considered slow K^+ channels [6], with $\tau_m \beta_{\mathrm{K}} \ll 1$. Here, we assume that v and w change on the same timescale, with $\tau_m \beta_{\mathrm{K}} = O(1)$. The number of open K^+ channels becomes an *external* state since it shows up as part of the deterministic dynamical system, while the number of open Na^+ channels is an *internal* state since it is averaged out in the deterministic limit.

A perturbation framework has been developed to study metastable activity in processes with noisy internal/external dynamics [1, 6, 11–13]. Two large parameters are present and necessary to reach a deterministic limit, and in order to obtain a single small parameter to carry out a systematic perturbation expansion, we define $\epsilon \ll 1$ such that

$$\beta_{\mathrm{Na}}^{-1} = \lambda_\beta \epsilon, \quad M^{-1} = \lambda_M \epsilon, \tag{7}$$

with $\lambda_\beta/\tau_m = O(1)$ and $\lambda_M/\tau_m = O(1)$. (We set $\lambda_\beta = 1$.) Of course, N could also be a large parameter, but taking the limit $N \to \infty$, $M \to \infty$ yields a different deterministic limit than the ML model (1). An alternative to our approach would be to take M and N to be large parameters, and this would significantly alter the following analysis. However, in the regime where $\beta_{\rm Na}$, M, and N are all large, we expect that either approach yields similar results. A more thorough exploration will apear elsewhere.

We use a WKB perturbation method to derive a uniformly accurate approximation of the stationary density [15]. The WKB approximation also tells us what path a stochastic trajectory is most likely to follow during a metastable transition (i.e., a path of maximum likelihood [4]). First, we assume that the stationary solution has the form

$$\hat{\rho}(v, w, n) = r(n|v, w) \exp\left[-\frac{1}{\epsilon}\Phi(v, w)\right], \tag{8}$$

where $\Phi(v, w)$ is referred to as the *quasipotential* and $r(n|v, w)$ is the conditional distribution for n given v, w. In the classic problem of exit in a double well potential, Φ is the double well potential. More broadly, Φ is a measure of how unlikely it is for a stochastic trajectory to reach a point in phase space. After substituting (8) into the right hand side of (4), taking the limit $t \to \infty$, and collecting terms in ϵ, we find at leading order,

$$\left[\frac{1}{\lambda_\beta}\mathbb{L}_{\rm Na} + p_v + h(v, w, p_w)\right] r(n|v, w) = 0, \tag{9}$$

where $p_v = \frac{\partial \Phi}{\partial v}$, and $p_w = \frac{\partial \Phi}{\partial w}$; and we define

$$h(v, w, p_w) = \frac{\beta_{\rm K}}{\lambda_M} \sum_{j=\pm} (e^{-j\lambda_M p_w} - 1)\widehat{\Omega}^j_{\rm K}(w|v) \tag{10}$$

where $\widehat{\Omega}^\pm_{\rm K}(w|v) \equiv \Omega^\pm_{\rm K}(Mw|v)/M$.

In order to solve (9) for Φ and r, we first take r to be of the form [1]

$$r(n|v, w) = \binom{N}{n} \left(\frac{1}{1+A}\right)^{N-n} \left(\frac{A}{1+A}\right)^n. \tag{11}$$

To determine A, we substitute (11) (alternatively, it is simpler to use $r = A^n/n!$) into (9) to obtain a consistency expression with two terms: one linear in n and one independent of n. From the former we obtain

$$A = a_{\rm Na}(v) - \frac{\lambda_\beta}{N}(p_v g(v, w) + h(v, w, p_w)), \tag{12}$$

where $g(v, w) = w f_{\rm K}(v) + f_{\rm leak}(v) + I_{\rm app}$. After substituting (12) into the remaining n-independent term, we obtain the nonlinear scalar PDE for Φ,

$$\mathcal{H}(v, w, \frac{\partial \Phi}{\partial v}, \frac{\partial \Phi}{\partial w}) = 0, \tag{13}$$

where

$$\begin{aligned}
&\mathcal{H}(v,w,p_w,p_v)\\
&\quad= -\frac{\lambda_\beta}{N}(1-x_\infty(v))g(v,w)(f_{\text{Na}}(v)+g(v,w))p_v^2\\
&\qquad+(x_\infty(v)f_{\text{Na}}(v)+g(v,w))p_v\\
&\qquad-\frac{\lambda_\beta}{N}(1-x_\infty(v))(2g(v,w)+f_{\text{Na}}(v))p_v h(v,w,p_w)\\
&\qquad+h(v,w,p_w)-\frac{\lambda_\beta}{N}(1-x_\infty(v))h(v,w,p_w)^2,
\end{aligned}$$

which can be solved using the method of characteristics.

Characteristics are curves $(\mathbf{x}(t),\mathbf{p}(t))$ (with $\mathbf{x}=(v,w)$ and $\mathbf{p}=(p_v,p_w)=\nabla_{\mathbf{x}}\Phi$) that satisfy the following Hamiltonian dynamical system,

$$\dot{\mathbf{x}}=\nabla_{\mathbf{p}}\mathcal{H}(\mathbf{x},\mathbf{p}),\quad \dot{\mathbf{p}}=-\nabla_{\mathbf{x}}\mathcal{H}(\mathbf{x},\mathbf{p}). \tag{14}$$

Note that the deterministic system (1) is recovered by setting $\mathbf{p}=0$. Characteristic projections, $\mathbf{x}(t)$, we refer to them as metastable trajectories, are paths of maximum likelihood leading away from the deterministic fixed point [4]. The *action*, $\Phi(t)$, satisfying $\dot{\Phi}(t)=\mathbf{p}(t)\cdot\nabla_{\mathbf{p}}\mathcal{H}(\mathbf{x}(t),\mathbf{p}(t))$, is a strictly increasing function of t, and the quasipotential is given by $\Phi(v,w)=\Phi(t)$ at the point $(v,w)=\mathbf{x}(t)$. Note that along deterministic trajectories, $\mathbf{p}=0$ and $\dot{\Phi}=0$. We solve (14) using numerical ODE integration [11], and we solve (13) on a uniform mesh using an ordered upwind finite difference method (OUM) [2].

3 Results

Surrounding the stable fixed point, Φ takes the shape of a potential well (see Fig. 2), with convex level curves (dashed lines). Once the Φ reaches a threshold, a point on the level curve looses smoothness forming a caustic. Metastable trajectories begin to overlap, and the solution $\Phi(v,w)$ loses uniqueness. Within this region, uniqueness is achieved at each point by minimizing the action over all metastable trajectories that pass through that point. Using the OUM method, we compute the quasipotential on a uniform 300×300 mesh, for mesh points such that $\Phi(v_i,w_j)<\Phi_{\max}\approx0.3$. (The remaining mesh points are not computed.) The caustic forms an incomplete boundary around most of the potential well region. The remaining boundary is the curve of constant $\Phi(v,w)=\Phi_c$, where $\Phi_c\approx0.258$ is the quasipotential at the caustic formation point (see thick dashed line in Fig. 2). We refer to this line as the *metastable separatrix*.

We identify SAP trajectories as those metastable trajectories that cross the separatrix. As shown in Fig. 3, SAP trajectories begin at the fixed point as a single trajectory and then fan out just before reaching the metastable

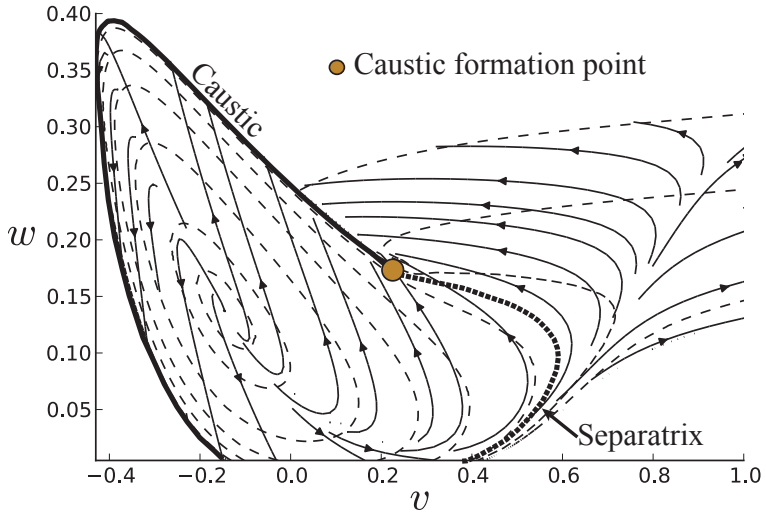

Figure 2: Level curves of the quasipotential (dashed curves) and metastable trajectories (streamlines). Parameter values are $N = M = 10$ and $\lambda_M = 1$.

separatrix (curve marked (S) in Fig. 3). After crossing the separatrix, all of the SAP trajectories eventually reach the caustic. Although all SAP trajectories are equally likely to reach the separatrix, they are not equally likely to reach the caustic. SAP trajectories become less likely the farther from the caustic formation point they are when reaching the caustic. Strictly speaking, the most probable SAP trajectory strikes the caustic formation point, but Φ increases by a very small amount in the shaded region of Fig. 3. (The maximum difference is $|\Delta\Phi| \approx 0.003$, and $|\Delta\Phi| / \Phi_c \approx 0.01$.) That is, $\dot{\Phi}(t) \ll 1$ since SAP trajectories are close to deterministic trajectories (black streamlines). Hence, the stationary density (8) (after normalization) is nearly flat in the shaded region, and all the SAP trajectories in this region are nearly equally likely.

The shaded region represents the most likely experimentally observable SAP trajectories; it excludes the small amplitude SAP trajectories that strike very close to the caustic formation point and the far less probable SAPs that reach the caustic above or behind the potential well region. The SAP trajectories that cover the shaded region cross a very small segment of the separatrix, the center of which acts much like a saddle point. We refer to this point as a metastable saddle. Most of the trajectories that cross the separatrix above the saddle are small amplitude SAPs that reach the caustic very close to the caustic formation point. Most of the trajectories that cross the separatrix bellow the saddle are large amplitude SAPs that are much less likely than those in the shaded region.

Based on the fast/slow analysis of the deterministic system, one might expect w to be approximately constant along SAP trajectories if K^+ channels

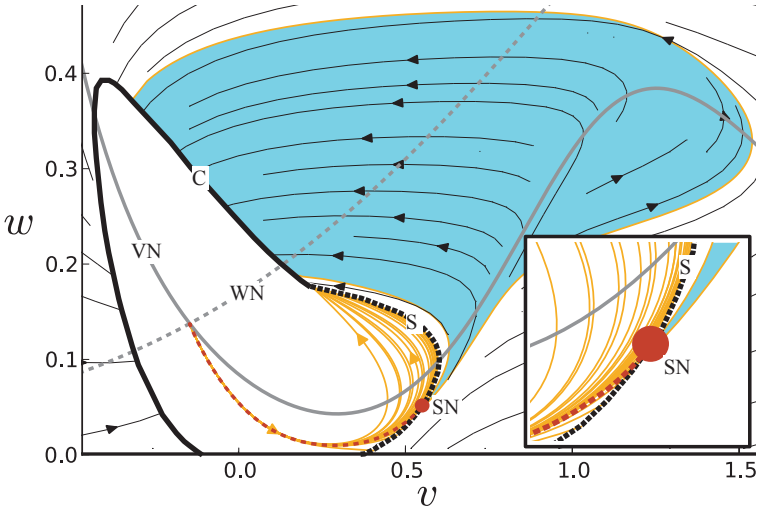

Figure 3: Orange curves are SAP trajectories, shown only up to the point where they reach the metastable separatrix (S). The dashed red curve is a SAP that crosses S near the metastable saddle (SN); it is not shown after it crosses the separatrix because all of the SAP trajectories in the shaded region are visually indistinguishable from the dashed red line before they reach S. The shaded region contains the most probable SAP trajectories; its lower and upper boundary are SAP trajectories that cross S near SN. The SAP trajectories in the shaded region are close to deterministic trajectories (black streamlines). Also shown are the caustic (C), v nullcline (VN), and w nullcline (WN). Parameters are the same as Fig. 2.

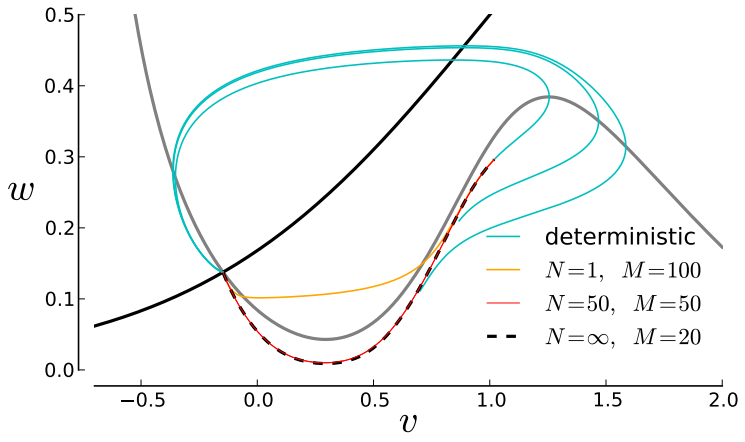

Figure 4: SAP trajectories for different values of M and N. Also shown (blue curves) are deterministic trajectories. We use $\lambda_M = 1/(\epsilon M)$ with $\epsilon = 0.1$.

open and close slowly. However, this expectation implies that the SAP trajectory is close to a time-reversed deterministic trajectory, which is correct only if the stationary density preserves detailed balance. Indeed, the behavior of w during a SAP depends strongly on how noisy the K^+ channels are. Recall that K^+ channel noise is controlled by M since w behaves deterministically in the limit $M \to \infty$. In Fig. 4, several SAP trajectories are shown for different values of M and N. Note that the position of the metastable separatrix and saddle (not shown) changes for each SAP shown in Fig. 4. If M is very large, w behaves deterministically and remains relatively constant during the SAP, and in this regime the fast/slow approximation might be valid. On the other hand, for most reasonable values of M (i.e., $M \approx N$), the K^+ conductance drops sharply so that v remains below the $\dot{v} = 0$ nullcline, and this is also true in the limit $N \to \infty$ where a SAP is driven entirely by K^+ channel noise (dashed curve Fig. 4).

Fluctuations in the slow recovery dynamics of K^+ channels significantly affect the spontaneous activity in the ML model. Since these effects change the effective energy barrier leading to a SAP, the spontaneous firing rate will depend strongly on the level of K^+ noise. There are more features of the Hodgkin-Huxley model—the sodium conductance has a slow inactivating component and ion channels have more complicated multi-state dynamics—to be considered in future work. Our analysis uses standard, systematic perturbation methods that can be applied to general stochastic excitable systems.

A Parameter values

Parameter values are $v_{\rm Na} = 120\text{mV}$, $g_{\rm Na} = 4.4\text{mS/cm}^2$, $v_{\rm K} = -84\text{mV}$, $g_{\rm K} = 8\text{mS/cm}^2$, $v_{\rm L} = -60\text{mV}$, $g_{\rm L} = 2\text{mS/cm}^2$, $C_{\rm m} = 20\mu\text{F/cm}^2$, $\beta_{\rm K} = 0.02\text{ms}^{-1}$, $I_{\rm app} = 0.06 C_{\rm m} v_{\rm eff}$, $\varphi = -0.1$, $v_{\rm eff} = 52.8\text{mV}$, $\gamma_{\rm Na} = 1.22/v_{\rm eff}$, $\kappa_{\rm Na} = -1.188 + 1.22 v_{\rm eff}$, $\gamma_{\rm K} = 0.8/v_{\rm eff}$, $\kappa_{\rm K} = 0.8 + 0.8 v_{\rm eff}$.

References

[1] P. C. Bressloff and J. M. Newby, *Metastability in a stochastic neural network modeled as a velocity jump markov process*, in press SIAM J. Appl. Dyn. Syst., (2013).

[2] M. Cameron, *Finding the quasipotential for nongradient sdes*, Physica D, 241 (2012), pp. 1532 – 1550.

[3] C. C. Chow and J. A. White, *Spontaneous action potentials due to channel fluctuations*, Biophys. J., 71 (1996), pp. 3013–3021.

[4] M. I. Freidlin and A. D. Wentzell, *Random Perturbations of Dynamical Systems*, Springer- Verlag, New York, 2nd edition ed., 1998.

[5] C. W. Gardiner, *Handbook of stochastic methods for physics, chemistry, and the natural sciences*, vol. v. 13, Springer-Verlag, Berlin, 1983.

[6] J. P. Keener and J. M. Newby, *Perturbation analysis of spontaneous action potential initiation by stochastic ion channels*, Phys. Rev. E, 84 (2011), p. 011918.

[7] J. P. Keener and J. Sneyd, *Mathematical physiology*, vol. 8 of Interdisciplinary applied mathematics, Springer, New York, NY, 2nd ed ed., 2009.

[8] I. A. Khovanov, A. V. Polovinkin, D. G. Luchinsky, and P. V. E. McClintock, *Noise-induced escape in an excitable system*, Phys. Rev. E, 87 (2013), p. 032116.

[9] B. Lindner, J. García-Ojalvo, A. Neiman, and L. Schimansky-Geier, *Effects of noise in excitable systems*, Physics Reports, 392 (2004), pp. 321 – 424.

[10] C. Morris and H. Lecar, *Voltage oscillations in the barnacle giant muscle fiber*, Biophys. J., 35 (1981), pp. 193–213.

[11] J. M. Newby, *Isolating intrinsic noise sources in a stochastic genetic switch*, Physical Biology, 9 (2012), p. 026002.

[12] J. M. Newby and J. Chapman, *Metastable behavior in markov processes with internal states*, Submitted, (2013).

[13] J. M. Newby and J. P. Keener, *An asymptotic analysis of the spatially inhomogeneous velocity-jump process*, Multiscale Model. Simul., 9 (2011), pp. 735–765.

[14] E. Schneidman, B. Freedman, and I. Segev, *Ion channel stochasticity may be critical in determining the reliability and precision of spike timing*, Neural Computation, 10 (1998), pp. 1679–1703.

[15] Z. Schuss, *Theory and applications of stochastic processes: an analytical approach*, vol. v. 170 of Applied mathematical sciences, Springer, New York, 2010.

[16] J. White, J. Rubinstein, and A. Kay, *Channel noise in neurons*, Trends Neurosci., 23 (2000), pp. 131–137.